

CHAPTER 56

Edema and Deep Vein Thrombosis

KEY TEACHING POINTS

- In patients with generalized edema, the most important physical finding is examination of the neck veins. If venous pressure is elevated, cardiopulmonary hypertension is the cause of the edema.
- In patients with unilateral leg edema suggestive of deep vein thrombosis, individual physical findings are largely inaccurate, but combinations of findings using the Wells rule accurately assess the probability of thrombosis as high, intermediate, or low.
- In patients with unilateral arm edema suggestive of deep vein thrombosis, combinations of findings using the Constans rule accurately distinguish those likely to have thrombosis from those unlikely to have it.

EDEMA

I. INTRODUCTION

Edema of a limb may occur because of increased venous pressure (e.g., venous insufficiency, congestive heart failure), increased vascular permeability (e.g., inflammation), decreased oncotic pressure (e.g., hypoalbuminemia), lymphatic obstruction (i.e., lymphedema), and deposition of additional tissue (e.g., lipedema). The most common causes of bilateral edema are congestive heart failure, chronic venous insufficiency, pulmonary hypertension, and drug-induced edema (e.g., nifedipine, amlodipine, or nonsteroidal antiinflammatory medications).¹ The most common causes of unilateral swelling of the leg are deep vein thrombosis, Baker cyst, and cellulitis (see later section).²⁻⁴

II. THE FINDINGS

The pitting characteristics of edema reflect the viscosity of the edema fluid, which in turn depends largely on its protein concentration.⁵⁻⁸ Edema fluid with low protein levels (e.g., hypoalbuminemia, congestive heart failure) pits easily and recovers relatively quickly compared with edema fluid that has higher protein levels (lymphedema, inflammatory edema).^{6,7} A clue to low-protein edema (i.e., edema associated with a serum albumin level less than 3.5 g/dL) is edema that pits easily with only 1 to 2 seconds of thumb pressure over the tibia, and then, after removal of the thumb, begins to recover within 2 to 3 seconds.⁸

Lymphedema is painless, firm edema that characteristically causes squaring of the toes and a dorsal hump on the foot. In contrast to venous edema, lymphedema

varies little during the day and ulceration is uncommon unless there is secondary infection. Even though lymphedema has high protein levels, clinical experience reveals that lymphedema does pit early in its course although it eventually becomes nonpitting, hard, and "woody" as secondary fibrosis ensues.^{5,9,10}

Lipedema consists of bilateral deposition of excess subcutaneous fatty tissue in the legs that does not pit with pressure and whose most characteristic feature is sparing of the feet.¹¹ Lipedema occurs exclusively in obese women.

III. CLINICAL SIGNIFICANCE

A. PITTING EDEMA

In patients with bilateral pitting edema of the legs, the most important diagnostic finding is the patient's venous pressure, estimated from examination of the neck veins. If the neck veins are abnormally distended, cardiac disease or pulmonary hypertension is at least partly responsible for the patient's edema; if they are normal, another cause is responsible, such as liver disease, nephrosis, chronic venous insufficiency, or one of the patient's medications. Clinicians' estimates of venous pressure are accurate, with studies showing that the finding of elevated neck veins predicts an abnormally increased central venous pressure (i.e., >8 cm H₂O) with a positive likelihood ratio (LR) of 8.9 (see Chapter 36).

In contrast, the finding of pitting edema by itself and without knowledge of the patient's venous pressure is an unreliable sign of cardiac disease. For example, in patients undergoing cardiac catheterization because of chest pain or dyspnea, the finding of edema (without knowledge of venous pressure) lacked any significant relationship with the patient's left heart pressures (see Chapter 48).

B. LYMPHEDEMA

Lymphedema is classified as *primary* (i.e., congenital abnormality of the lymphatic systems) or *secondary* (damage to the lymphatics from previous radiation or surgery, malignant obstruction, or recurrent episodes of cellulitis).¹⁰ Primary lymphedema begins before the age of 40 years, may be bilateral (50% of cases), and affects women 10 times more often than men.¹² Secondary lymphedema from infection, radiation, or surgery affects men and women of all ages, is usually unilateral, and is preceded by the characteristic history. Malignant obstruction affects patients older than 40 years and is almost always unilateral (>95% of cases).¹² The most common cause of malignant lymphedema in the leg is metastatic prostate carcinoma in men and lymphoma in women.¹² Lymphedema of the arm is almost always due to breast cancer, either the tumor itself or combined treatment with surgery and radiation.¹³

DEEP VEIN THROMBOSIS

I. INTRODUCTION

Deep vein thrombosis of the leg is conventionally divided into *proximal* thrombosis (popliteal vein and above) and *distal* thrombosis (calf veins). Several studies have shown that only proximal thrombi are associated with clinically significant pulmonary emboli, and thus only these thrombi require treatment with anticoagulation.¹⁴

In patients with acutely painful and swollen calves, accurate diagnosis is essential, not only because untreated proximal thrombi may cause fatal pulmonary emboli, but also because inappropriate administration of anticoagulation to persons without proximal thrombi unnecessarily risks life-threatening hemorrhage.

II. THE FINDINGS

A. INSPECTION AND PALPATION

The most important signs of vein thrombosis are tenderness and swelling. Calf asymmetry of more than 1.5 cm is abnormal, indicating significant edema of the larger limb or atrophy of the smaller one.¹⁵

Other traditional signs associated with deep vein thrombosis are a palpable cord, dilated superficial veins, Homans sign, skin erythema, and altered skin temperature (both coolness and warmth have been proposed by different authorities). However, the basis for these signs seems dubious. Because large muscles and dense fascial tissues encompass the deep veins of the legs, concealing them from the examiner's eyes and hands, it is difficult to conceive how a clinician could ever palpate the cord of a thrombosed *deep* vein. The increased collateral flow around an obstruction could make the superficial veins more conspicuous, but skin surface temperature and color reflect blood flow and vessel size of the minute vessels of the dermis,¹⁶ which would not necessarily be different after venous obstruction.

B. HOMANS SIGN

In his extensive writings about venous thrombosis, the American surgeon John Homans contrasted two forms of the disease: bland thrombosis of the calf veins, which caused few symptoms other than mild swelling and pain, and iliofemoral thrombophlebitis (*phlegmasia alba dolens*), which caused generalized leg edema and cyanosis.¹⁷⁻¹⁹ Homans believed that most pulmonary emboli originated in the bland calf thrombi and that, once diagnosed, the disorder should be treated by femoral vein ligation to prevent pulmonary emboli (anticoagulation was not yet being used). In 1941 Homans proposed that the *dorsiflexion sign*, defined as "discomfort behind the knee on forced dorsiflexion of the foot," was a sign of these difficult-to-diagnose calf thrombi.¹⁸ Although contemporaries called the sign *Homans sign*,²⁰ Homans never did and instead later credited another clinician for making the original description.²¹

Surgeons soon learned that there were many examples of a false-positive Homans sign (i.e., positive dorsiflexion sign but no clot found at surgery),^{20,22} and in 1944 Homans redefined the positive response, stating that "discomfort need have no part in the reaction." Eventually, Homans became unenthusiastic about the sign,^{23,24} and has been quoted as saying "if you wanted to name a sign after me, why didn't you pick a good one?"²⁵

C. PSEUDOTHROMBOPHLEBITIS

In a large series of patients presenting with suspected deep vein thrombosis, only one out of every four or five patients actually has the diagnosis.²⁶⁻³⁰ An important mimic of deep vein thrombosis (i.e., *pseudothrombophlebitis*) is Baker cyst, which is a distended gastrocnemius-semimembranosus bursa that has dissected or ruptured into the calf or is compressing the popliteal vein.^{31,32} A telltale sign of this disorder (and any other cause of calf hematoma) is crescent-shaped ecchymosis near either malleolus.^{33,34}

III. CLINICAL SIGNIFICANCE

A. INDIVIDUAL FINDINGS

EBM Box 56.1 presents the diagnostic accuracy of physical signs for deep vein thrombosis of the lower extremity, as applied to thousands of patients with acute calf pain, swelling, or both. Although some studies recruited outpatients^{26,36,38-41,43-50} and others both inpatients and outpatients,^{28,29,42} the accuracy of individual signs is the same whether or not inpatients are included in the analysis. In almost all studies, “deep vein thrombosis” refers only to proximal thrombosis (popliteal vein or higher),^{29,35,36,38-41,43-50} although a few studies included patients with proximal vein or isolated calf vein thrombosis (however, in these studies, only 15% to 29% had isolated calf thrombosis).^{28,37,42} Most studies excluded patients with symptoms suggesting pulmonary embolism.

According to these studies, only the findings of asymmetric calf swelling (≥ 2 cm difference, LR = 2.1), superficial vein dilation (LR = 1.6), swelling of the entire leg (LR = 1.5), and asymmetric skin warmth (LR = 1.4) increase the probability of thrombosis, although the discriminatory value of all these signs is slight. The presence or absence of erythema, tenderness, skin coolness, palpable cord, and Homans sign lack diagnostic value. As expected, the finding of superficial thrombophlebitis (i.e., visibly inflamed and tender subcutaneous veins) also lacks any relationship to pathology in the deep veins. No individual finding convincingly decreases the probability of thrombosis (i.e., no LR <0.5).

These same studies show that certain risk factors assist diagnosis, most importantly the presence of active cancer (sensitivity 7% to 39%, specificity 90% to 97%, positive LR = 2.9).^{26,28,29,38-41,43,51} The findings of “recent immobilization” or “recent surgery” both increase the probability of deep venous thrombosis a smaller amount (positive LR for each finding is 1.6).

B. COMBINED FINDINGS

Given the meager accuracy of individual findings, Wells and others developed a simple scoring scheme (**Table 56.1**) that combines findings, stratifying patients into groups of low, moderate, or high probability for deep vein thrombosis of the leg.²⁶ The findings entering his model were all demonstrated to be independent predictors in an earlier analysis.^{27,52} This model has now been validated in many studies enrolling more than 6000 patients with suspected deep venous thrombosis: a low pre-test probability (0 or fewer points by this model) decreases the probability of deep vein thrombosis (LR = 0.2; **EBM Box 56.2**), and a high pre-test probability (3 or more points) significantly increases the probability of deep vein thrombosis (LR = 5.9). The finding of a moderate pre-test probability is diagnostically unhelpful.

The Wells score has been tested mostly in outpatients and may be less accurate in inpatients.⁵⁷ In addition, Wells’s original rule was later modified by adding one extra variable (“previous documented deep vein thrombosis”) to the original rule (earning one additional point if present). This *modified Wells rule* is also accurate, whether it is trichotomized as the original rule (i.e., low probability [0 or fewer points], LR = 0.3; intermediate probability [1 or 2 points], LR not significant; and high probability [3 or more points], LR = 3.9)^{43,56,58} or is dichotomized into deep venous thrombosis “likely” (2 or more points, LR = 2.1) or “unlikely” (<2 points, LR = 0.3).⁵⁹

If the clinical probability is low using any of these Wells rules and a quantitative D-dimer measurement is normal, the probability of deep vein thrombosis is so low that anticoagulants and further testing may safely be withheld. Randomized studies

**EBM BOX 56.1****Lower Extremity Deep Vein Thrombosis***

Finding (Reference) [†]	Sensitivity (%)	Specificity (%)	Likelihood Ratio [‡] if Finding Is	
			Present	Absent
Inspection				
Any calf or ankle swelling ^{23,24,29,35-39}	41-90	8-74	1.2	0.7
Asymmetric calf swelling, ≥2 cm difference ^{28,40}	61-67	69-71	2.1	0.5
Swelling of entire leg ^{29,38,39,41}	34-57	58-80	1.5	0.8
Superficial venous dilation ^{24,38,39,41,42}	28-33	79-85	1.6	0.9
Erythema ^{35,36,42}	16-48	61-87	NS	NS
Superficial thrombophlebitis ³⁷	5	95	NS	NS
Palpation				
Tenderness ^{23,24,35-39,41,42}	19-85	10-80	NS	NS
Asymmetric skin coolness ²⁴	42	63	NS	NS
Asymmetric skin warmth ^{35,42}	29-71	51-77	1.4	NS
Palpable cord ^{29,42}	15-30	73-85	NS	NS
Other Tests				
Homans sign ^{23,24,29,35-37,42}	10-54	39-89	NS	NS

*Diagnostic standard: for deep venous thrombosis, positive contrast venography^{23,24,29,35-37,42} or compression ultrasonography.^{28,38-41}

†Definition of findings: all findings refer to the symptomatic leg.

‡Likelihood ratio (LR) if finding present = positive LR; LR if finding absent = negative LR.
NS, Not significant.

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DEEP VENOUS THROMBOSIS

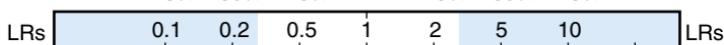
Probability

Decrease

-45% -30% -15%

Increase

+15% +30% +45%



Absence of asymmetrical calf swelling

Asymmetrical calf swelling, ≥2 cm difference
Superficial vein dilation
Swelling of entire leg
Asymmetrical skin warmth

TABLE 56.1 Wells Scoring Scheme for Pre-Test Probability of Deep Vein Thrombosis^{26*}

Clinical Feature	Points
RISK FACTORS	
Active cancer	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden >3 days or major surgery, within 4 weeks	1
SIGNS	
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Asymmetric calf swelling (>3 cm difference, 10 cm below tibial tuberosity)	1
Asymmetric pitting edema	1
Collateral superficial veins (non-varicose)	1
ALTERNATIVE DIAGNOSIS	
Alternative diagnosis as likely or more likely than deep venous thrombosis	-2

*Interpretation of score: high probability if 3 points or more, moderate probability if 1 or 2 points, and low probability if 0 points or less.

EBM BOX 56.2

Lower Extremity Deep Vein Thrombosis (Wells Score)*

Pre-Test Probability ^{26,30,44,46-50,53-56†}	Sensitivity (%)	Specificity (%)	Positive LR [‡]
Low pre-test probability	2-29	24-77	0.2
Moderate pre-test probability	13-46	—	NS
High pre-test probability	38-87	71-99	5.9

*Diagnostic standard: for deep vein thrombosis, proximal vein clot by compression ultrasonography,^{26,30,43,44,46-50,54,55} sometimes with contrast venography.^{26,54} In some studies,^{43,47,49,54,55} deep venous thrombosis was excluded without compression ultrasonography in patients with low clinical risk, normal D-dimer assay, and absence of venous thromboembolism during 3 months of follow-up.

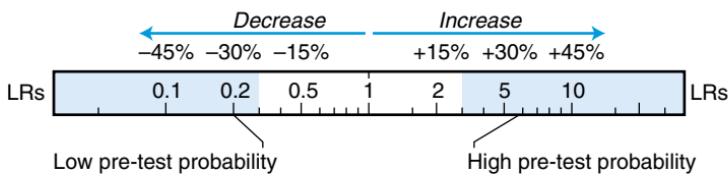
†Definition of findings: for pre-test probability, see Table 56.1.

‡Likelihood ratio (LR) if finding present = positive LR; LR if finding absent = negative LR.
NS, Not significant.

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DEEP VENOUS THROMBOSIS (LEG)—WELL'S SCORE

Probability



**EBM BOX 56.3****Upper Extremity Deep Vein Thrombosis^{60,61*}**

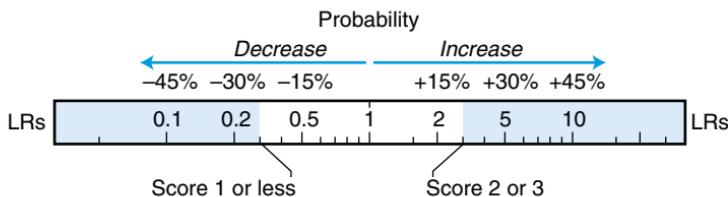
Finding [†]	Sensitivity (%)	Specificity (%)	Positive LR
Constans score 1 or less, detecting arm DVT	12-42	15-37	0.3
Constans score 2 or 3, detecting arm DVT	58-88	63-85	3.0

*Diagnostic standard: for arm deep vein thrombosis, compression ultrasonography.

†Definition of findings: for Constans score, see the text.

DVT, Deep venous thrombosis.

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DEEP VENOUS THROMBOSIS (ARM)—CONSTANS SCORE

show that this approach is as accurate and safe as performing compression ultrasonography in all patients.⁵⁹

C. DIAGNOSING UPPER EXTREMITY DEEP VENOUS THROMBOSIS

Constans and others have derived and validated a bedside rule to diagnose deep venous thrombosis of the upper extremity.⁶⁰ According to this rule, the clinician adds one point for each of three clinical findings—(1) venous material (i.e., catheter, pacemaker, or access device in a subclavian or jugular vein), (2) pitting edema of arm, (3) localized pain of the arm—and then subtracts one point if another diagnosis is at least as plausible as arm deep venous thrombosis (possible scores thus range from -1 to 3). A Constans score of 1 or less decreases the probability of arm thrombosis (LR = 0.3; **EBM Box 56.3**), and a score of 2 or 3 increases probability of thrombosis (LR = 3).

The references for this chapter can be found on www.expertconsult.com.

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